"Neurologic Basis of Autism"

Autism Course for PGY 2 Child and Adolescent Psychiatry Fellows

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Pittsburgh, PA
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1943-1980

- Described as a syndrome in 1943, 1944
- Thought to be psychogenic in etiology until 1970
- Originally described as a broad range of severity with emphasis on high functioning: 60/40 split
- By 1970, syndrome reduced to moderate MR w/ echolalia & self-stimulatory repetitive behavior
- Originally distinguished from schizophrenia, then classified under childhood psychoses until 1980

Where We Were In 1980

- Autism introduced as a category in DSM/ICD
- No diagnostic instruments
- All cases thought to be caused by other disorders
- Focal brain dysfunction
- Single primary cognitive or sensory deficit
- Very rare disorder: 2/10,000
- Mental disorder

Pervasive Developmental Disorders (DSM)
*Autism Spectrum Disorders (Informal)

DSM-III (1980)

- Infantile autism
- Childhood onset pervasive development disorder
- Childhood onset PDD NOS

DSM-III-R (1987): Autistic Disorder
PDDNOS

DSM-IV (1994): Pervasive Developmental Disorders

- *Autistic Disorder
- *Asperger's Disorder
- *Pervasive Developmental Disorder NOS
- Childhood Disintegrative Disorder
- Rett's Disorder

Diagnostic Instruments

- Autism Diagnostic Interview-Revised
- Autism Diagnostic Observation Schedule
- Expert clinical opinion for confirmation
- Research reliability of administration & scoring of instruments- initial & ongoing
- Expert clinical opinion rules out cases but does not over-ride instruments to include cases

How Research Findings Changed The Disorder: Autism 1990

- Diagnostic methods resulted in recognition that 90-95% of cases idiopathic e.g. autism existed as a disorder in its own right & genetic in origin
- Dawning recognition of neural systems origin
- Increasing documentation of much higher prevalence 1-2/10,000 to 1/100 for ASD
- Recognition that cognitive & neurologic deficits involved higher order abilities in HFAs, not basic abilities, e.g. cerebral hemispheres and cortical systems in particular

Prevalence 1/166
2002-2006

Description	Baird et al[1]	Chakrabarti & Fombonne[2]	Brick Township, NJ[3]	Chakrabarti & Fombonne[4]
Autism	30.8/10,000	16.8/10,000	40.5/10,000	22.0/10,000
Other ASDs	27.1/10,000	45.8/10,000	26.9/10,000	36.7/10,000
Total for ASDs	57.9/10,000	62.6/10,000	67.4/10,000	58.7/10,000
Total for ASDs	1/170	1/170	1/150	1/170

- 1Baird et al, 2000
- 2Chakrabarti & Fombonne, 2001
- 3Bertrand et al, 2001
- 4Chakrabarti & Fombonne et al, 2001

Prevalence 1/150 or 1/100
February 2007

Description	Kadesjo, et al[1] 1999	Baird, et al[2] 2006	CDC[3] 2007
Autism	60/10,000	38.9/10,000	
Other ASDs	48/10,000	77.2/10,000	
Total for ASDs[4]	108/10,000	116.1/10,000	66/10,000
Total for ASDs	1/100	1/100	1/150

[1]Kadesjo et al, JADD, 29:4, 327-331

[2]Baird et al, The Lancet 368, 210-215 206

[3]ADDM Network, MMWR 02-09-07; 12-28

[4]This number was 20/10,000 in 1980

Estimates of Expressive Language Level at Age 9
151 Autism Participants

Lord et al Arch Gen Psych 2006; 63: 694-701

Description	Chicago	North Carolina
Complex sentences (ADOS Module 3)	40.9%	39.6%
Sentences but not fluent (ADOS Module 2)	35.3	28.9
Words but not sentences (ADOS Module 1; ADI-R = 1)	10.5	16.8
No or few consistent words (ADI-R=2)	14.3	14.4

Behavioral Neurology Appraisal

- Complex behavior abnormalities
- Cognitive impairments w/ MR in 50-60%
- Seizures in 30%
- Absence of blindness, deafness, long tract signs

Synthesis: association cortex with sparing of primary sensori-motor cortices and white matter

Caveat: no focal signs- distributed neural systems disorder

Neurologic Approach to Deciphering Disease

Neurologists' approach to understanding disease process is to examine all impaired AND intact abilities to define common principles or characteristics of the underlying disease process.

Disease Processes

- Infectious disease
- Vascular disease
- Tumor or mass
- Toxins
- Developmental processes

Developmental Neurobiologic Processes

- Organogenesis (basic form of the nervous system)
- Neuronal proliferation
- Glial proliferation, migration
- Neuronal migration
- Neuronal organization
- Myelination

Discriminant Function Analysis: Domains Without Deficits[3]

Domain	Tests Passing Tolerance	Percent Correct	Kappa[1]
Attention	Letter Cancellation; Number Cancellation	66.70	0.33
Sensory Perception	Finger Tip Writing; Luria-Nebraska Sharp/Dull Tactile Scale item	64.40	0.29
Simple Language	K-TEA Reading; K-TEA Spelling WRMT-R Attack; Controlled Oral Word Association	71.20	0.42[2]
Simple Memory	CVLT Trial 1	65.20	0.30
Visuo-Spatial	WAIS-R Block Design	56.10	0.12

[1]Kappa below .40 indicates poor agreement beyond chance
[2]Significant *Kappa* reflects superior performance by autistic subjects
[3] Based on 33 individually age, IQ, gender matched pairs of subjects

Discriminant Function Analysis[1]: Domains With Deficits

Domain	Tests Passing Tolerance	Percent Correct	Kappa
Motor	Grooved Pegboard; Trail Making A	75.80	0.52
Complex Language	K-TEA Reading Comprehension; Verbal Absurdities; Token Test	72.70	0.45
Complex Memory	Nonverbal Selective Reminding-Consistent Long Term Retrieval; WMS-R Story Recall-Delayed Recall; Rey-Osterrieth Figure-Delayed Recall	77.30	0.55
Reasoning	20 Questions; Picture Absurdities; Trail Making B	75.8	0.52

[1]Based on 33 individually matched pairs of autistic & control subjects (Neuropsychologic Functioning in Autism: Profile of a Complex Information Processing Disorder, *JINS*, 3:303-316, 1997)

The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

Intact or Enhanced

- Attention
- Sensory Perception
- Elementary Motor
- Simple Memory
- Formal Language
- Rule-learning
- Visuospatial processing

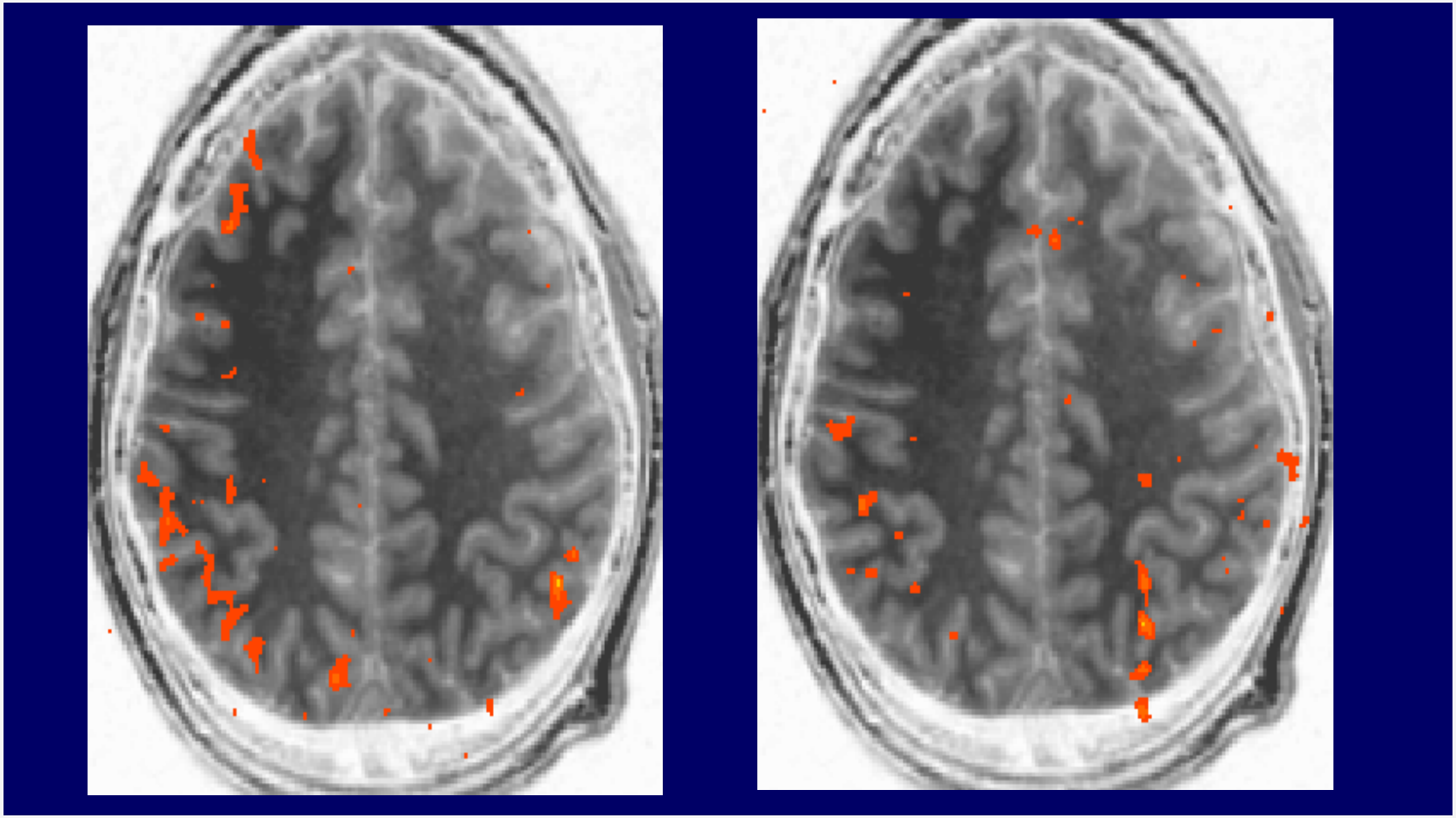
Cognitive Weaknesses

- Complex Sensory
- Complex Motor
- Complex Memory
- Complex Language
- Concept-formation
- Face Recognition

What Does The Profile Mean About Neurologic Function & Neural Circuitry?

- Simpler processing & abilities are intact/enhanced
- Information processing capacity is limited- integrative processing & higher order cognitive abilities are disproportionately impacted
- Inference: higher order circuitry is under developed- they are reliant on lower order circuitry & basic cognitive abilities to function.

fMRI Activation During a Spatial Working Memory Task (Courtesy John Sweeney)



Control Group

Autism Group

Converting Communication Failure to Success Pink Pill-Blue Pill

Jim was admitted for possible mania. He was agitated and had been sending money to television evangelists and became preoccupied with sin and going to hell. He carried and read from the Bible constantly. The psychiatrists attempted daily to convince him to try lithium but he refused. His reason was that he took lithium on June 4, 1978 and he got a stomach ache. He went to the clinic and a scene ensued. Staff yelled at him. No amount of REASONING worked to change his mind, until he was told and SHOWN there were now two forms of lithium - one was pink and one was blue. He took the “bad blue” before, but this time he would take the “good pink”. He immediately agreed to lithium. The deterioration in his behavior was the result of losing his job for asking a woman a question about her clothing, which was interpreted as sexual harassment. All structure was gone from his life and he became disorganized but not manic. Socially-emotionally he was three.

"Neurotypical people have a social sense right from the time they're born." p. 32

"My ability to function in the world & develop social relationships has been learned solely through my intellect…and use of my visualization skills. I have learned by rote how to act in different situations. Using my visualization ability, I observe myself from a distance in each situation. I call this my "little scientist in the corner"… I take note of the details that make up the situations just like a scientist observes an experiment. All that data gets put on my computer hard drive memory...

Social Interactions contd

How I “tackle social situations is very much a scientific approach, based on observation, analysis, conclusions.”

She learned by reading articles and trial and error, keeping what worked and discarding what did not. She was 40 before she had enough data in her data base to improve.

- A Major Omission From All Cognitive Theories

Dr. Temple Grandin

"For some of us with ASDs, the emotional-relatedness physical or biochemical circuitry is missing- no matter how hard we try, it's a bridge that may never be built because some of the basic building materials are missing."

"Romantic relationships have a level of social complexity that I still don't understand today and I consciously choose not to participate in them. My way of thinking and functioning does not describe everyone on the spectrum."

Autism: A Disorder of Affective Contact

Capacity to experience, understand & regulate emotions also fundamentally altered and not appreciated, despite frequent imaging studies of amygdala

Many verbal ASD individuals socially-emotionally as young as 12-18 months to 3-5 years of age- causes major symptms

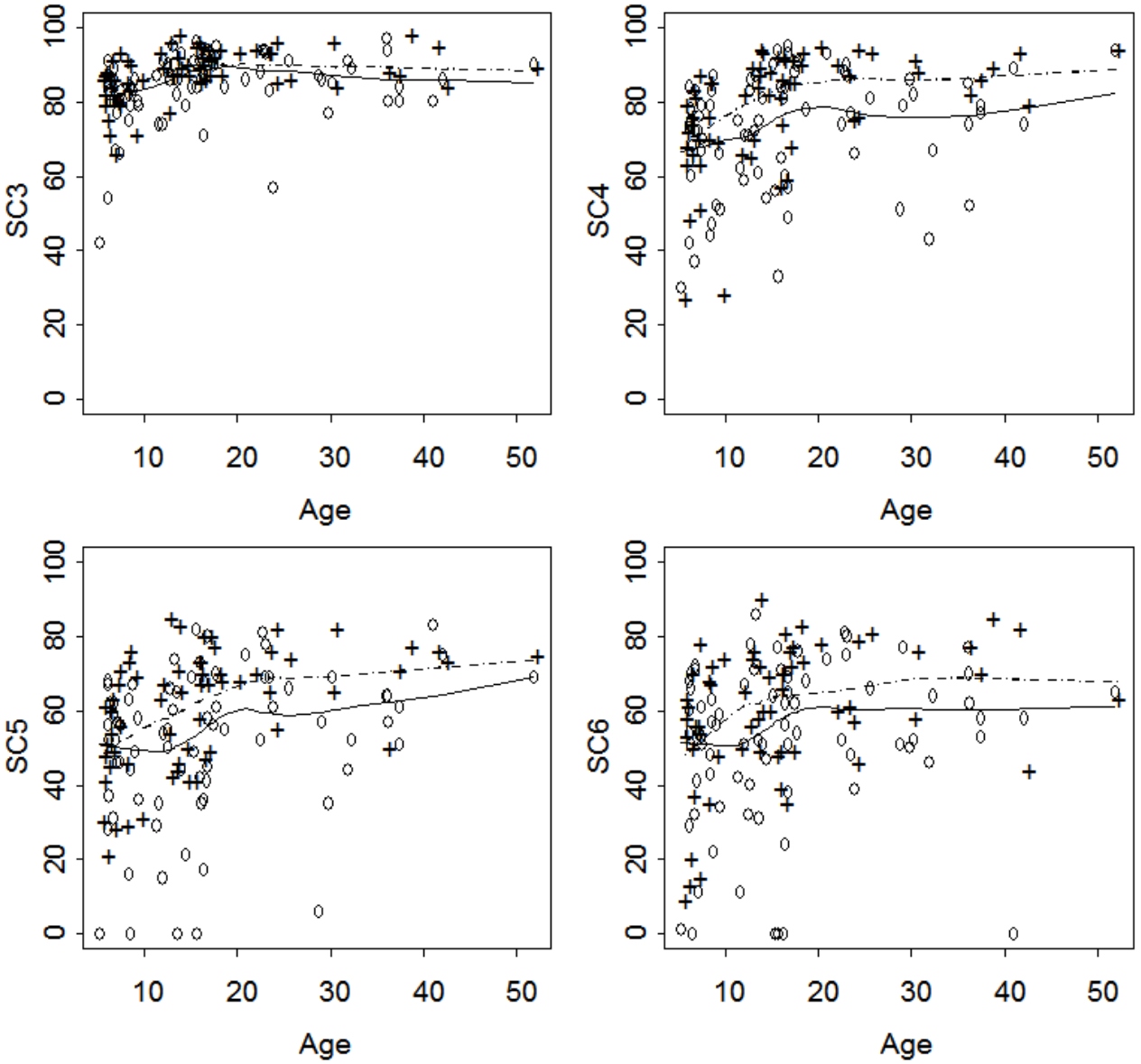
Studies of amydala-cortical interactions, social motivation, tolerance of frustration ongoing

Emotional Immaturity: Also Not in DSM Criteria

Postural Control: Impaired Integration of Joint, Position, Vestibular, & Visual Input

Minshew et al. (2004) Underdevelopment of the postural control system in autism. Neurology; 63:2056-2061.

- In the last three panels, SC4-SC6, the difficulty emerges as platform motion is introduced. These panels demonstrate delayed development and a failure of the autism group to achieve adult levels.
- Measures for autistic subjects (circles) and control subjects (crosses) and locally smoothed curves (solid line for autistic subjects, broken line for control subjects). R-square for fits: 0.198 (SC3), 0.164 (SC4), 0.175 (SC5), and 0.170 (SC6).


SC3
SC4
SC5
SC6
Age
0
20
40
60
80
100
10
20
30
40
50

Additional Implication of Profile: Triad to Brain-Wide

- Autism is defined on the basis of abnormalities in social, communication and imaginative play, and restricted interests-repetitive behavior.
- The neuropsychologic and postural findings define deficits considerably beyond this triad, suggesting a more brain-wide disturbance in information processing.

Williams et al. 2006. 12: 279-298

Concept Formation Impairments Present Globally
All rely on prototype formation mechanisms

- Motor concept learning
- Memory dependent on strategies
- Story creation or theme identification
- Face recognition
- Face affect recognition
- Strategy formation, problem solving

How the mind organizes information, Or not in the case of autism

Cognitively the problem is with prototype formation and

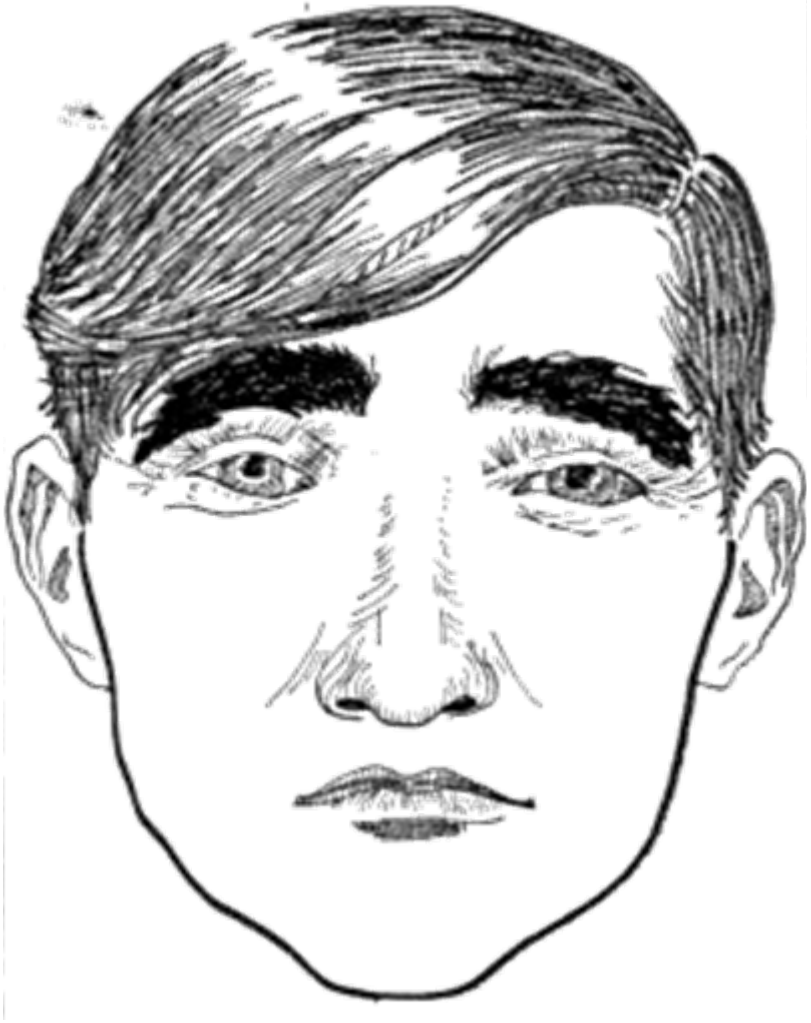
automatic processes

as opposed to conscious, verbally mediated reasoning.

Pitt Infant and Toddler Development Center

- Abilities that adults take for granted that normally develop in infancy and toddlerhood:
- For example:
  - ✓ Our abilities to recognize faces and emotional expressions
  - ✓ Our abilities to understand the difference between basic categories in the world– cats, dogs, lions …

Which of these is the best example of a dog?



Which of the following two faces looks more familiar to you?

1

2

TYPICAL

SOMEWHAT TYPICAL

ATYPICAL

Cognitive Research in 5-50 year old HFAs

- The way individuals with autism come to learn about both the world and people is different from individuals who do not have autism.
- There are core differences in the way they learn categorical information and acquire “expertise”

Gasgeb, Strauss, & Minshew. Child Dev 2006; 77: 1717-1729

The New Neurobiology of Autism: Key Questions That Were Confronted in 90's-

- Distributed or focal?
- Neocortical or subcortical?
- White matter or gray matter?
- Intra- and inter- hemispheric?

Head Growth in Autism

Lainhart et al. Am J Med Genet 2006, 140A:2257-2274

- Group mean 60-70%
- Onset accelerated growth at 12 months w/ 15-20% macrocephaly by 4-5 years
- Growth decelerates and plateaus so that brain volume “normalizes” in childhood, though subset remain macrocephalic throughout life
- Important to recognize that HC>HT is not universal in autism and HC=HT and HC<HT growth trajectories compatible with autism

Increased Brain Volume in Autism: What does it Mean?

- Group TBV paralleled group HC findings; increase related to intracerebral white matter, and cortical gray matter depending on parcellation
- Herbert et al. parcellated white matter into inner and outer radiate white matter: increased volume of outer intra-hemispheric short and medium range cortico-cortical connections; no increase in inter-hemispheric or cortical-subcortical connections.

Herbert et al. Brain 2003; 126: 1182-92

Synthesis of Brain Volume Studies: Developmental Disturbance in Cortical Connectivity

- Major role for white matter but without accompanying long tract signs and thus the difference between acquired and devel. disorders
- Disturbance in connectivity
- Increased white matter volume was associated with dysfunction not increased function
- Inter-hemispheric white matter e.g. corpus callosum was not involved in the same process

Minshew & Williams, Arch Neurol in press

Why does WM damage from other causes not result in autism?

Because autism is a disorder of neurons, not axons, myelin, or glia

- And because autism is a disorder of early brain development not of damage to already developed structures

Minicolumn Abnormalities in Autism: Evidence of Cortical Involvement

- First substantive abnormalities of cerebral cortex
- Radially oriented arrays of pyramidal neurons, interneurons, axons and dendrites
- Smallest radial unit of information processing; then macrocolumns and receptive fields?
- Bilateral abnormalities in areas 3, 4, 9, 17, 21, 22
- Increased #, narrower, reduced neuropil space (inhibitory neurons), neurons small

Casanova et al. Acta Neuropathol 2006; 112:287-303

Additional Evidence of Cortical Involvement

- Proton MRS study of 3-4 yr olds with autism, DD, TD: reduced choline compound concentrations and transverse relaxation, suggestion decreased cellularity or density in ASD but not DD or TD
- T2 relaxation in same children prolonged in GM but not WM in ASD but in both GM and WM in DD. Selective involvement of GM interpreted as abnormal developmental process in ASD

Friedman et al. Arch Gen Psych 2006; 63:786—794;
Petropoulous et al. Neurology 2006; 67:632-636

Additional Evidence of Cortical Involvement

- 26 males 6-17 years IQ>70 w/ autism & 26 controls
- Proton MRs revealed significantly lower levels of cortical gray matter NAA and glutamate-glutamine that were widespread in cerebral lobes and cerebellum
- Conclusion: widespread reduction in gray matter neuronal integrity and dysfunction of cortical and cerebellar glutamatergic neurons

DeVito et al Biol Psychiatry 2007; 61:465-473

Genes, Multi-Organs and Environment

- Unsupported theories have proposed that gi or immune dysfunction caused CNS dysfunction
- However, neurologic disorders are typically multi-organ disorders
- No evidence of environmental cause of overwhelming majority of cases of autism.
- Regarding vaccines and other environmental issues, Paul Offitt's book on Autism's False Prophet's is a must read.

Genes and Multi-Organ Involvement

- 2.27 relative risk of autism diagnosis conferred by the CC genotype MET receptor tyrosine kinase. MET signaling is involved in neocortical and cerebellar development, immune function, and gastrointestinal repair, consistent with the multi-organ symptoms reported in autism

Campbell et al. PNAS 2006, 45: 16834-16839

Neural Basis of Clinical Symptoms

- fMRI studies have been the window on the mind and the path to understanding of complex behavior and higher order cognition

- Extensive studies- social cognition system, emotion system, mirror neuron system, gaze processing, motion processing, face processing, …

Cortical activation & synchronization during sentence comprehension in HFA subjects

Marcel Just
Vlad Cherkassky
Tim Keller
Nancy Minshew

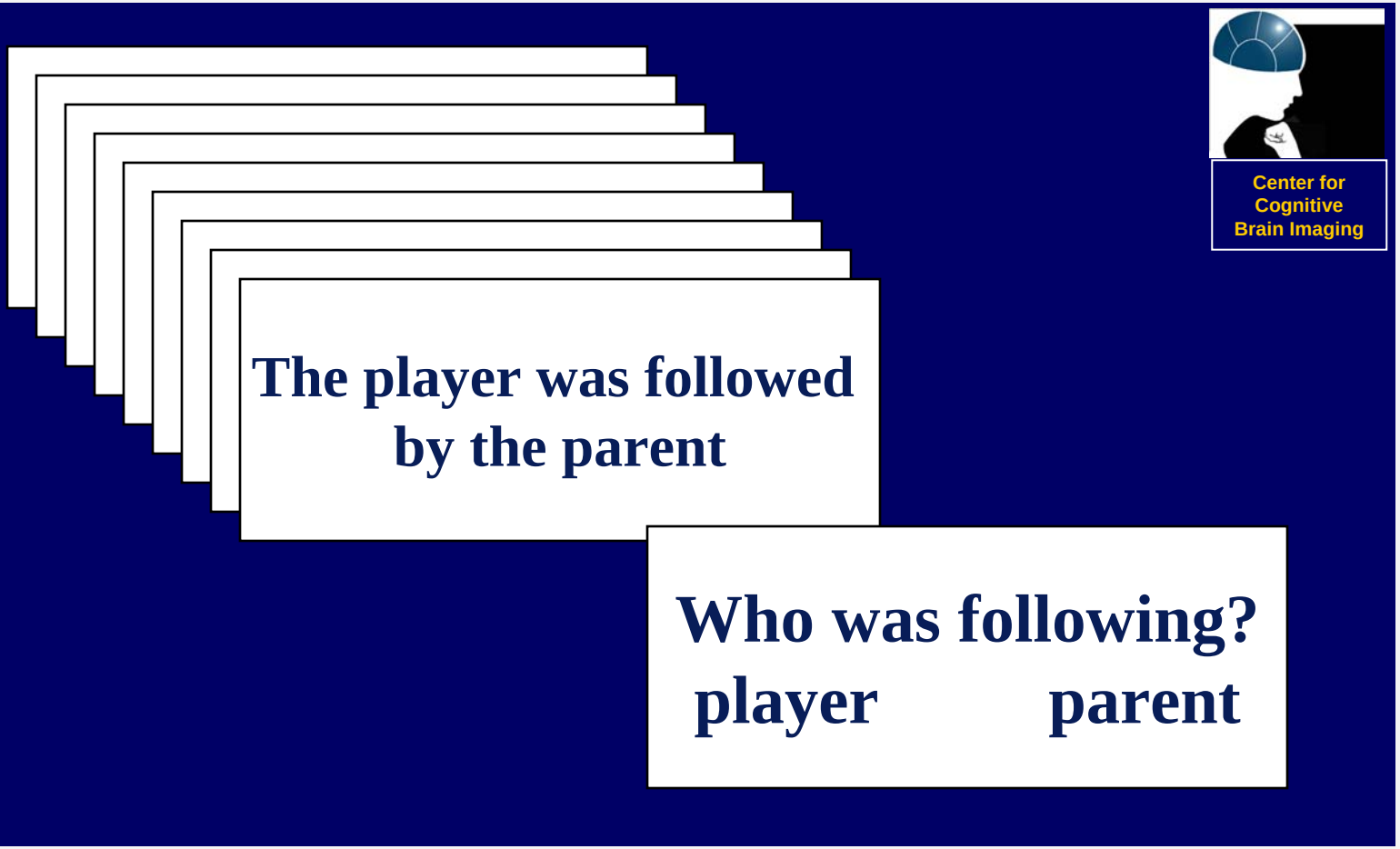
Center for Cognitive
Brain Imaging
Carnegie Mellon

Just et al. 2004, Brain 127: 1811-1821

Language Profile in HFA

- Superior to age-, IQ-, gender- matched controls on word & non-word decoding, spelling, vocabulary, fluency
- Inferior to controls on comprehension of sentences, idioms, metaphors, stories

Sentence reading task and comprehension probe



Brain activation during sentence comprehension in autism In Brain, 2004

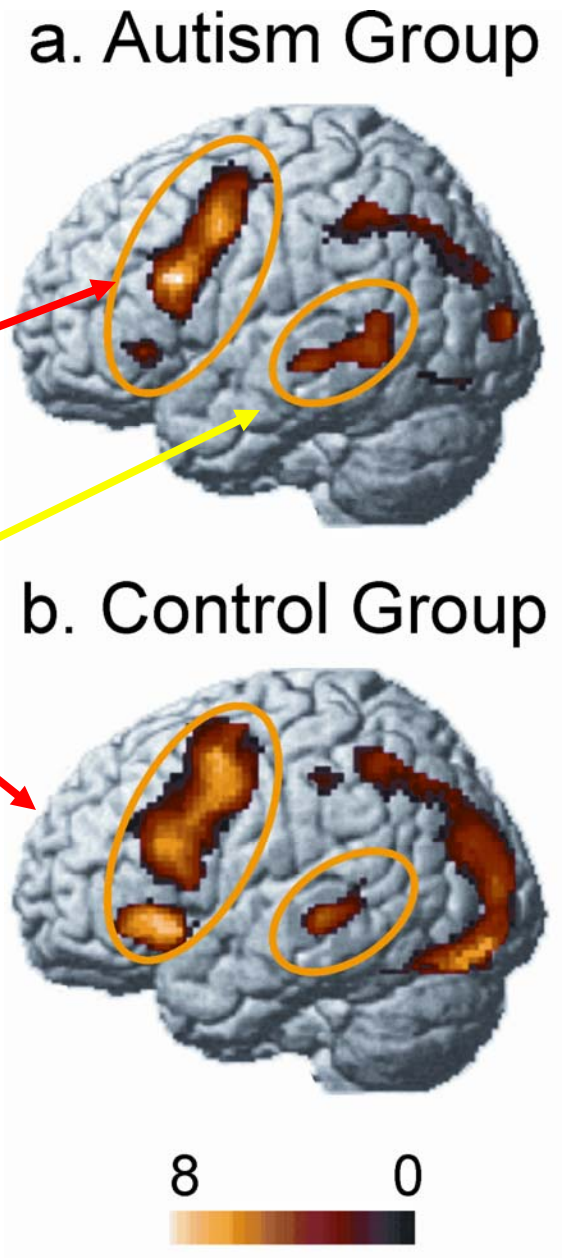
Autism group has less activation in **Broca's area**

- *(a sentence integration area)*

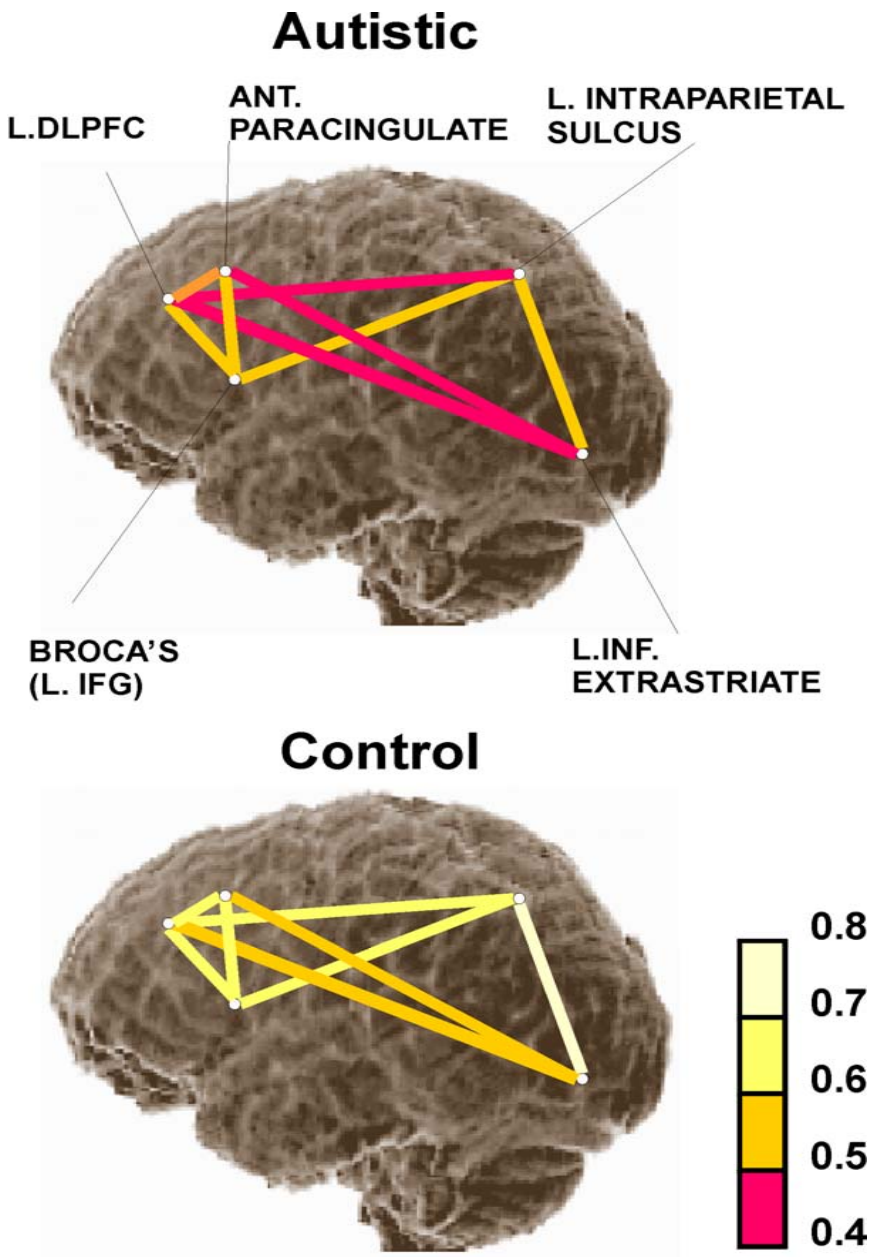
than the control group and more in **Wernicke's area**

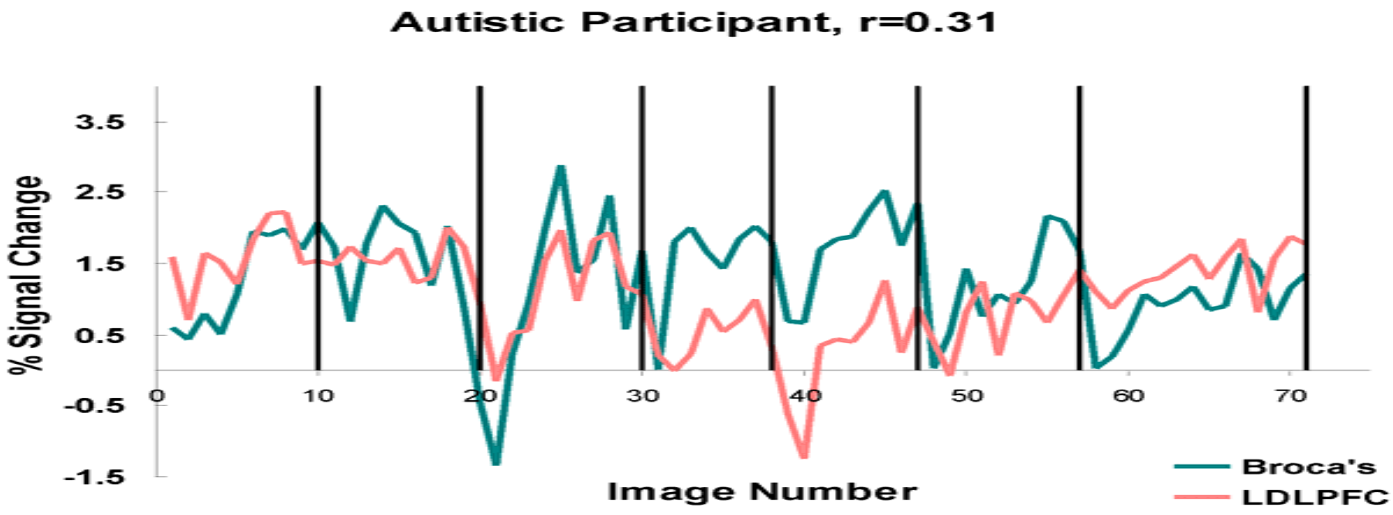
- *(a word processing area)*

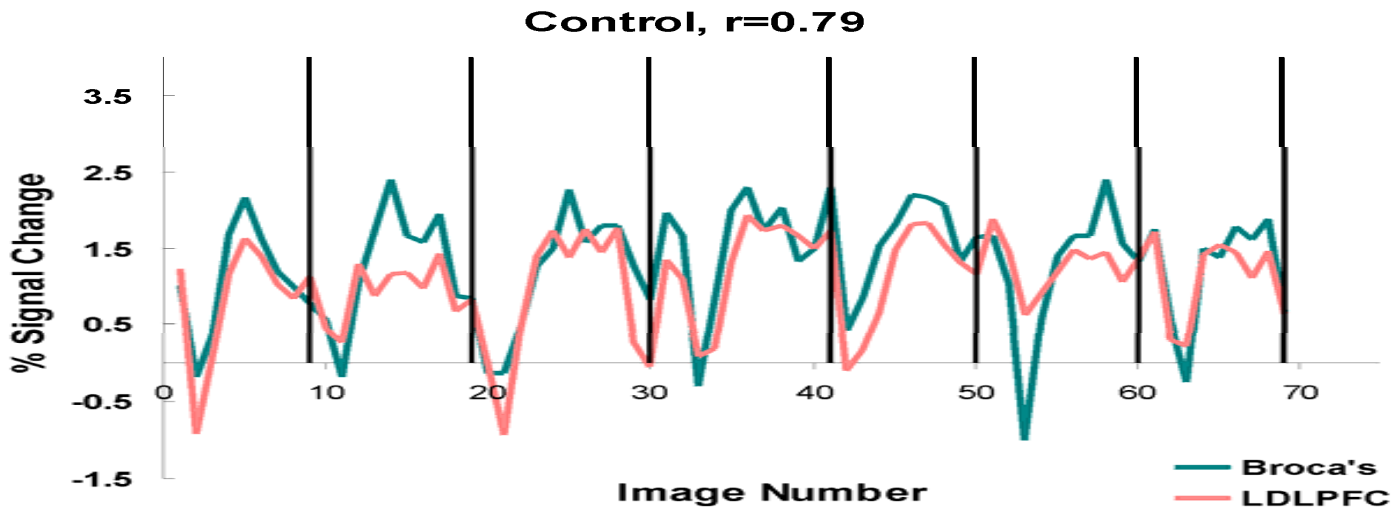
Results are consistent with poorer comprehension of complex sentences, coupled with good word reading (spelling bee champs)



Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)



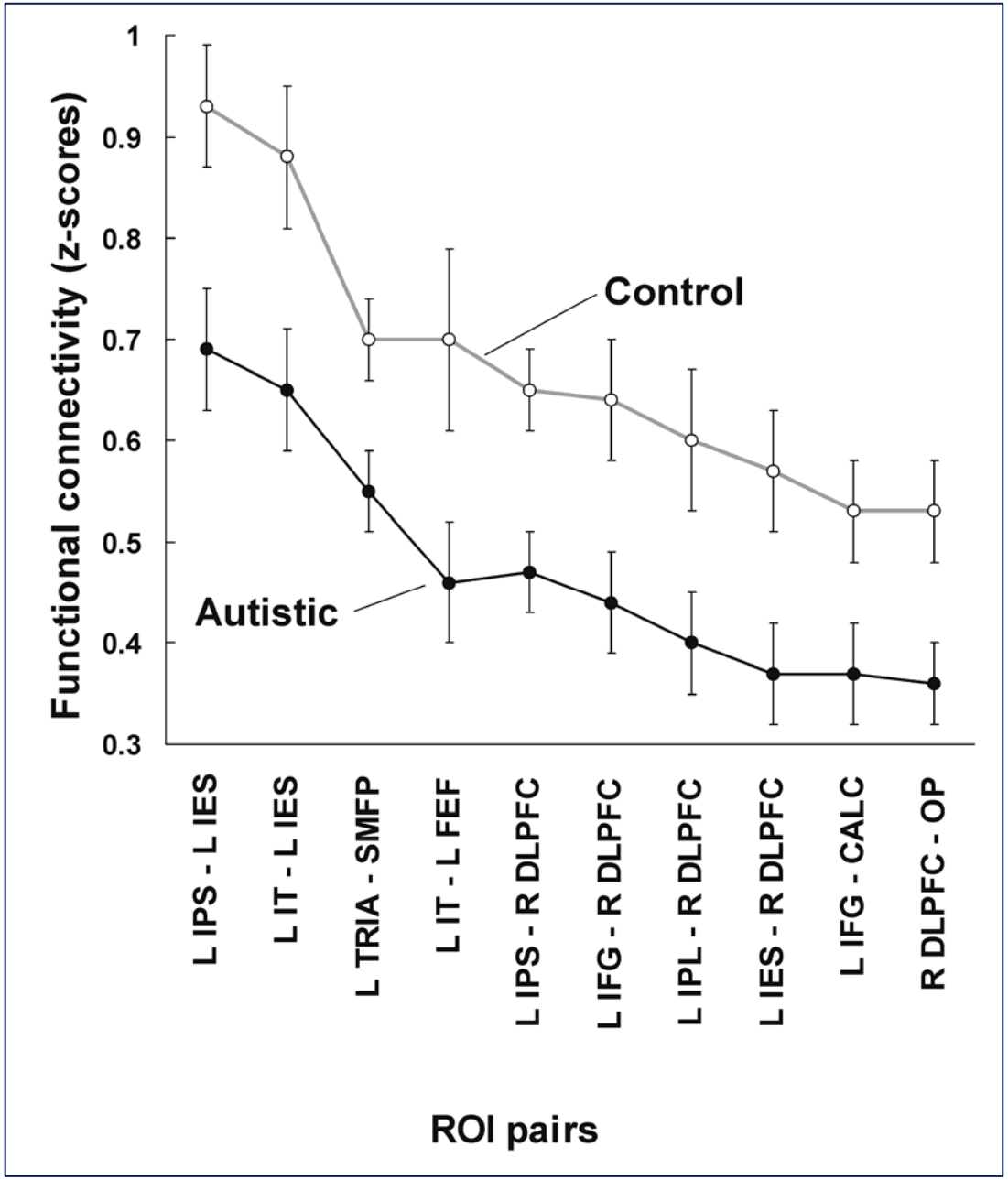




Functional Connectivity

The activation in two cortical areas can be less synchronized (upper panel) or more synchronized (lower panel) for different people

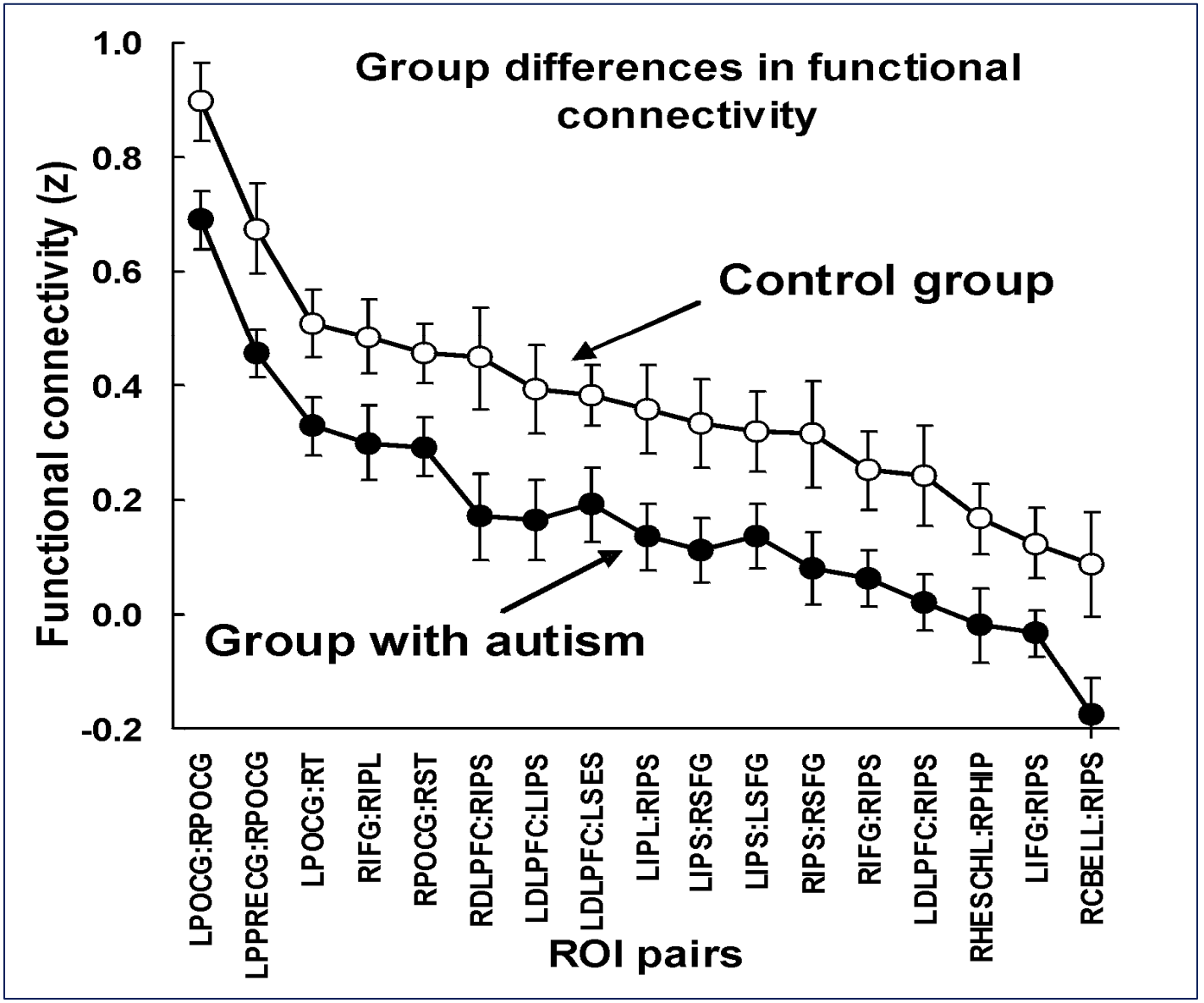
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order



Functional Underconnectivity: fMRI of the Tower of London

Marcel Just
Nancy Minshew
Tim Keller
Vlad Cherkassky
Rajesh Kana

Just et al., 2006 [Epub ahead of print], Cereb Cortex


Group differences in functional connectivity
Functional connectivity (z)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
Control group
Group with autism
LPOCG:RPOCG
LPPRECG:RPOCG
LPOCG:RT
RIFG:RIPL
RPOCG:RST
RDLPFC:RIPS
LDLPFC:LIPS
LDLPFC:LSES
LIPL:RIPS
LIPS:RSFG
LIPS:LSFG
RIPS:RSFG
RIFG:RIPS
LDLPFC:RIPS
RHESCHL:RPHP
LIFG:RIPS
RCBELL:RIPS
ROI pairs

fMRI of N-back Letter Task in Autism

Hideya Koshino
Patricia Carpenter
Nancy Minshew
Vlad Cherkassky
Tim Keller
Marcel Just

NeuroImage 2005; 24:810-821

N-Back Results: Alternate Cognitive & Neural Strategies in Autism

- Autism group used visually oriented processing of letters as visual-graphical codes
- Controls converted letter to verbal-phonological codes
- Autism group relied on lower level visuospatial analysis, and the large scale brain network has different organization from normals *(see factor analysis)*

Common Features of fMRI Studies of Brain Connectivity in Autism

- Some emphasize underconnectivity with frontal cortex
- A more accurate view may be of unimodal with polymodal cortex or of cortical connections
- Increased posterior activation-compensatory
- Reduced inter-hemispheric connectivity? Primary? Or Secondary?

Transforming Findings

1. A disorder of complex information processing
2. A disorder of brain cortical connectivity
3. Autism as a disorder of dysregulated growth of the cerebral hemispheres-gray and white matter but not corpus callosum-a neuron disorder
4. CNV in simplex; synapse-related genes in simplex & multiplex families
5. Selective gene expression will explain pattern of brain involvement and variability

Where Are We In 2009?

- 20-25 genes have been discovered in last 5-10 years that account for 15-20% of cases of ASD; most are rare genes but common genes are now being reported
- Selective cortical unconnectivity is accepted as a major theme of pathophysiology as is early dysregulation of brain growth
- Multiple processes of brain growth implicated including neuronal organization, migration and perhaps proliferation.

Clarification of Onset & Genetic: Communicating Science to the Public

- Many non-traumatic child neurologic disorders present “out of the blue”.
- A recent example at CNS meeting-neuronal ceroid lipofucshinosis, uniformly fatal, not responsive to bone marrow transplant, thus a candidate for stem cell therapy.

  3 forms: neonatal, infantile, juvenile.
- DNA: day to day director of life; may come with faults with different decay rates-faulty light bulbs or time bombs present from birth